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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/686,871	10/16/2003	Mark Czekaj	DEAV1999S005USCIP	7413

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EXAMINER	
MCKENZIE, THOMAS C	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 01/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/686,871	CZEKAJ ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie, Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2005* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *26-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to an election filed on 10/28/05. There are twenty-nine claims pending and twenty-five under consideration. Claims 1-24 are compound claims. Claim 25 is a composition claim. This is the first action on the merits. The application concerns some 2-substituted N-carbonyl)-pyrrolidine compounds and compositions thereof.

Election/Restrictions

2. Applicant's election with traverse of Group I in the paper of 10/28/05 is acknowledged. The traversal is on the ground(s) that no search burden is present. This is not found persuasive because according to the MPEP 803 "For purposes of the initial requirement, a serious burden on the examiner may be *prima facie* shown if the examiner shows by appropriate explanation of separate classification, or separate status in the art, or a different field of search as defined in MPEP § 808.02. That *prima facie* showing may be rebutted by appropriate showings or evidence by the applicant." The Examiner showed that Groups I-VII are in differing classes and subclass and Applicants made no showing that the classification analysis was in error. The requirement is still deemed proper and is therefore made FINAL.

3. Claims 26-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable

generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 10/28/05.

4. Objection is made to claims 1-9, 11-23, and 25 as containing non-elected subject matter. The claims are drawn to multiple inventions for reasons set forth in the above requirement for restriction. The claimed compounds, compositions, and methods that employ them present a variable core. Formula (I) contains compounds drawn to the non-elected inventions. Limitation of the ring A in formula (I) to the elected pyrrolidine compounds will overcome this objection.

Oath/Declaration

5. Applicants' comments about the difficulties of obtaining the signature of inventor Klein are noted. The present file contains a declaration for 10/686,871 signed by inventors Czekai and Pauls but not by inventor Klein. The file also contains a declaration for 10/143,190 signed by all three inventors. This application presents a claim for subject matter not originally claimed or embraced in the statement of the invention. Since 10/686,871 is a CIP, a new declaration by inventor Klein is required which references the present, 10/686,871, and application. A supplemental oath or declaration is required under 37 CFR 1.67. The new oath or declaration must properly identify the application of which it is to form a part, preferably by application number and filing date in the body of the oath or declaration. See MPEP §§ 602.01 and 602.02. If inventor Klein cannot be

located, Applicants are reminded of CFR § 1.47, "Filing when an inventor refuses to sign or cannot be reached". Section (c) of this rule contains an exception for continuation or divisional applications but not for CIP's.

Claim Objections

6. Claim 14 objected to because of the following informalities: should not the second word in line 2 of the claim be "is" not "as". Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts, N-oxides, and the specific acid bioisosteres listed in lines 9-13, page 5 of the specification of the claimed compounds, does not reasonably provide enablement for making solvates, prodrugs, and acid bioisosteres generally of the claimed compounds. The specification does not enable any person skilled in the art of synthetic organic chemistry to make the invention commensurate in scope with these claims. "The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of

direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. In the present case the important factors leading to a conclusion of undue experimentation are the lack of guidance in the specification of how to make these derivatives, the absence of any working example of a formed solvate, prodrug, or acid bioisostere, the lack of predictability in the art, and the broad scope of the claims.

b) The second paragraph, page 22 defines the term solvate but gives no direction as to how they might be formed or characterized. The first paragraph, page 5 gives examples of the intended acid bioisosteres but the passage uses open language. What additional acid bioisosteres are intended, what are their structures and how might they be prepared? The paragraph bridging pages 20 to 21 defines the properties of the desired prodrugs but gives no structures or methods of preparation.

c) There is no working example of any solvate, acid bioisostere, or prodrug formed. The claims are drawn to solvates, yet the numerous examples presented all failed to produce a solvate. These cannot be simply willed into existence. As

was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly.

g) The state of the art is that is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is their compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometery of the formed

solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. In the same paragraph on page 365 West (Solid State Chemistry) explains that it is possible to make meta-stable non-equilibrium solvates, further clouding what Applicants mean by the word solvate. Compared with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stabile region of the solvate.

Wolff (Medicinal Chemistry) summarizes the state of the prodrug art. The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modern Pharmaceutics) in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug.

h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula (I) as well as the presently unknown list of solvents

embraced by the term "solvate", the unknown list of acid bioisosteres, and the unknown list of intended prodrug derivatives. Thus, the scope is broad.

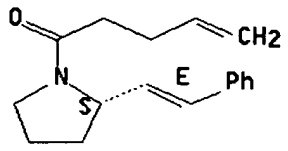
MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

Claim Rejections - 35 USC § 102

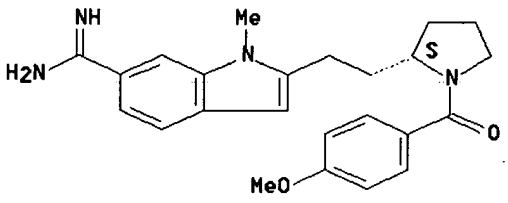
8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 5, 6, 9, and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Arisawa (Synlett). The compound shown below fits formula (I) with A = pyrrolidinyl, R^1 = H, the dotted line = a double bond, Z^1 = phenyl, and R^2 = 1-buten-4-yl. It has Registry Number 198218-79-0 and is found in Table 1, page 1179 of the reference. It is compound **1h**.

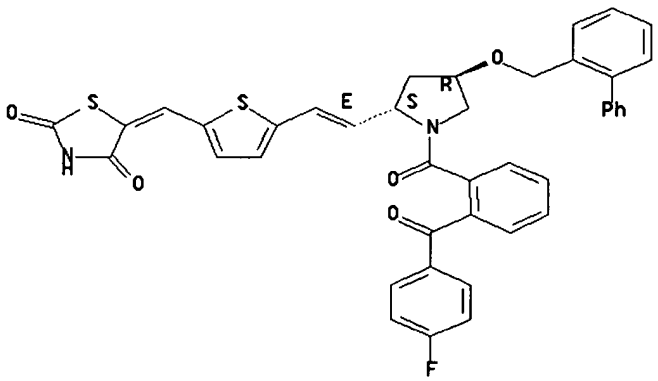


9. Claims 1-6, 9-12, 14, 19, 21, 22, and 25 rejected under 35 U.S.C. 102(b) as being anticipated by Sang (WO 97/45424 A1). There are over 250 species in this reference, which anticipate Applicants' claims including the compound shown below. The compound shown below fits formula (I) with A = pyrrolidinyl, R^1 = H, the dotted line = a single bond, Z^1 = the heteroaryl group indol-2-yl substituted by 6-(aminoiminomethyl) and 1-methyl, and R^2 = phenyl substituted by 4-methoxy. It has Registry Number 200182-50-9 and is found in lines 12-19, page 67 of the reference. It is Example 11. The other anticipatory compounds are found through out pages 53-226. Compositions are taught in claims 4-6 of the reference. Thus, the present claim 25 is taught



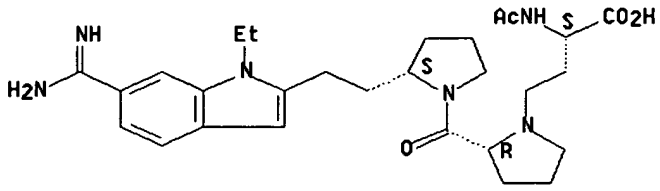
10. Claims 1, 5, 6, 9, 10, 12, and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Fumihiko (WO 98/33797 A1). There are 8 species in this reference, which anticipate Applicants' claims including the compound shown below. The

compound shown below fits formula (I) with A = pyrrolidinyl substituted by 4-([1,1'-biphenyl]-2-ylmethoxy), R^1 = H, the dotted line = a double bond, Z^1 = the heteroaryl group 2-thienyl substituted by (2,4-dioxo-5-thiazolidinylidene)methyl, and R^2 = phenyl substituted by 2-(4-fluorobenzoyl). It has Registry Number 211297-59-5 and is found in Table 19, page 100 of the reference. It is compound E-7. The other anticipatory compounds are E1-E6 and E8 on the same page.



11. Claims 1-3, 5, 6, 9, 10, 19, and 21-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Fumihiko (JP 11246554 A2). There are 8 species in this reference, which anticipate Applicants' claims including the compound shown below. The compound shown below fits formula (I) with A = pyrrolidinyl, R^1 = H, the dotted line = a single bond, Z^1 = the heteroaryl group indol-2-yl substituted by 6-(aminoiminomethyl) and 1-ethyl, and R^2 = propyl substituted by 3-acetylamino and carboxyl, It has Registry Number 243666-97-9 and is found in the table on

page 6 of the reference. It is compound I-1. The other anticipatory compounds are I-2 to I-7 and example 20.



Conclusion

12. Information regarding the status of an application should be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free). Please direct general inquiries to the receptionist whose telephone number is (703) 308-1235.

13. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas McKenzie, Ph.D. whose telephone number is (571) 272-0670. The FAX number for amendments is (571) 273-8300. The PTO presently encourages all applicants to communicate by FAX. The

Examiner is available from 9:00am to 5:30pm, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, please contact James O. Wilson, acting SPE of Art Unit 1624, at (571)-272-0661.

Thomas C. McKenzie, Ph.D.
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TCMcK
January 24, 2006